PATENT SPECIFICATION

952,194

NO DRAWINGS

952,194

Inventors: DAVID JACK, ROBERT GEOFFREY WILLIAM SPICKETT and GRAHAM JOHN DURANT

Date of filing Complete Specification: Dec. 5, 1961.

Application Date: Dec. 23, 1960. No. 44284/60.

Complete Specification Published: March 11, 1964.

Index at acceptance:—C2 C(2A2, 2A3, 2A5, 2A7, 2A8, 2A9, 2A12, 2R15, 2R16, 2R18, 2S16, 2S21, 2T16)

International Classification:—C 07 c, d

COMPLETE SPECIFICATION

New Guanidine Derivatives and processes for preparing

PATENTS ACT, 1949

SPECIFICATION NO. 952,194

In pursuance of Section 8 of the Patents Act, 1949, the Specification has been amended in the following manner:-

Page 4, *delete* line "43"

Page 4, *for* Claims "10 to 13" *read* "9 to 12" inclusive

Page 4, line 51, *for* "1 to 9" *read* "1 to 8"

Page 4, line 53, *for* "Claim 12" *read* "Claim 11"

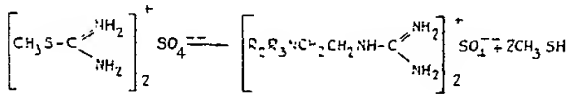
Reference has been directed, in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to Patent No. 1,005.728

THE PATENT OFFICE,
10th May, 1966

D 70693/10

II

and may be prepared by treatment of an appropriately substituted aminoethylamine with an isothiouronium salt, e.g. S-methylisothiouronium sulphate; viz.



III

When R_1 in formula I is an amino group, the guanidine derivatives of the invention are substituted aminoethylamino-guanidines having the general formula: —

[*Price 4s. 6d.*]

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International Classification:—C 07 c, d

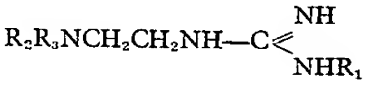
COMPLETE SPECIFICATION

New Guanidine Derivatives and processes for preparing the same

We, SMITH KLINE & FRENCH LABORATORIES LIMITED, a British Company, of Welwyn Garden City, Hertfordshire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to new guanidine derivatives and to processes for preparing the same.

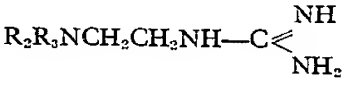
According to the present invention, there are provided new guanidine derivatives represented by the general formula:



I

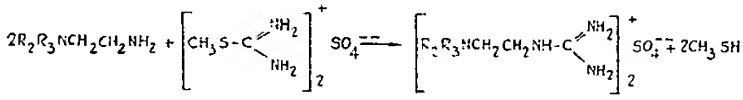
and pharmaceutically acceptable acid addition salts thereof, wherein R_1 is hydrogen or an amino group and wherein (a) when R_1 is hydrogen, R_2 is a methyl group and R_3 is a *cyclo*-heptyl or *cyclo*-octyl group, and (b) when R_1 is an amino group, R_2 and R_3 are joined together to form with the nitrogen atom a hexahydro-1-azepinyl group or an octahydro-1-azocinyl group.

When R_1 in formula I is hydrogen, the guanidine derivatives of the invention are substituted aminoethylguanidines having the general formula:



II

and may be prepared by treatment of an appropriately substituted aminoethylamine with an isothiouronium salt, e.g. S-methylisothiouronium sulphate; viz.



III

When R_1 in formula I is an amino group, the guanidine derivatives of the invention are substituted aminoethylamino-guanidines having the general formula: —

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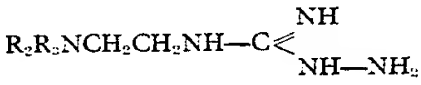
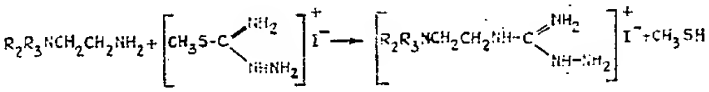


IV

and may be prepared by treatment of an appropriately substituted aminoethylamine with S-methyl-isothio-semicarbazide hydriodide, viz.



III

The guanidine salts obtained by either of the foregoing processes may, if desired, be converted into the corresponding free base by any suitable known method, e.g. by treatment with an alcoholic solution of a base.

The substituted aminoethylamines (formula III) may be prepared by treatment of the corresponding secondary amine with chloroacetonitrile in the presence of anhydrous potassium carbonate and by reducing the resulting cyanomethylamine with lithium aluminium hydride, viz.

The new guanidine derivatives of the invention have been found to possess varied pharmacological activity in the animal body. In particular, it has been found that these compounds block the autonomic sympathetic nervous system, as evidenced by the relaxation of the nictitating membrane of the unanaesthetised cat, and also have hypotensive activity, as evidenced by their effectiveness in producing a prolonged lowering of the blood pressure of the anaesthetised cat.

The pharmacologically active compounds of the invention will usually be administered in practice as a pharmaceutical composition generally in a suitable dosage unit form, said composition comprising the active guanidine derivative in an amount sufficient to produce the desired pharmacological effect, together with one or more pharmaceutical diluents and/or excipients. The dosage unit may be in liquid or solid form, and may be administered either orally or parenterally.

The following Examples illustrate the invention.

Example 1

Preparation of N-amino-N^1-[2-hexahydro-1-azepinyl-ethyl]-guanidine hydriodide

To a solution of 13.65 g. of S-methyl-iso-thiosemicarbazide hydriodide in ethanol (100 ml.) was added hexahydro-1-azepinyl-ethylamine (10.0 g.) and the reaction mixture was heated under reflux for 18 hours. The solution was concentrated *in vacuo* to low bulk (20 ml.) and set aside in the cold for 2 hours. The solid deposited (14.8 g.) was recrystallised from iso-propanol affording N-amino-N^1-[2-(hexahydro-1-azepinyl) - ethyl] - guanidine hydriodide, m.p. 97—98°C. Yield 11.8 g. (62% theoretical).

The starting material in the above reaction was prepared as follows: To a mixture of hexamethylenimine (250 g.) dry toluene (500 ml.) and anhydrous potassium carbonate (620 g.), chloroacetonitrile (210 g.) was added slowly with mechanical stirring. The mixture was heated under reflux for 30 hours with stirring. After cooling, filtering and concentrating under reduced pressure, the liquid residue was distilled giving (hexahydro-1-azepinyl)-methyl cyanide, b.p. 104—110°C./15 mm. Refractionation gave 273 g. (81% theoretical), b.p. 59—61°C./0.4 mm.

To a suspension of 25.1 g. of lithium aluminium hydride in 200 ml. of dry ether was slowly added a solution of the (hexahydro-1-azepinyl)-methyl cyanide (91 g.) in 150 ml. of dry ether, while cooling and stirring. Stirring was continued for 1¼ hours at room temperature. In succession were added wet ether (200 ml.), water (25 ml.), 20% sodium hydroxide (23 ml.) and water (88 ml.) with cooling and rapid stirring. The reaction mixture was filtered, dried (with potassium carbonate) and concentrated

under reduced pressure. The residual liquid was fractionated *in vacuo*, affording 2-(hexahydro-1-azepinyl)-ethylamine, b.p. 83—86°C./15 mm. (72 g.).

EXAMPLE 2

Preparation of β-(N-methyl-N-*cyclo*-heptyl-amino)-ethyl-guanidine sulphate.

To a solution of 4.45 g. S-methylisothiouronium sulphate in ethanol (200 ml.), N-methyl-N-*cyclo*heptylamino-ethylamine (5 g.) was added. The mixture was heated under reflux for 20 hours and then cooled. The solid deposited was filtered and recrystallised from iso-propanol. Yield of β - (N - methyl - N - *cyclo*heptylamino) - ethyl - guanidine sulphate 6.4 g., (83% theoretical), m.p. 230°C. (decomp.).

The starting material in the above reaction was prepared as follows: *Cyclo*-heptanone (36.4 g.) was added to 50 ml. of 33% ethanolic methylamine and the solution was added to 0.2 g. of reduced platinum oxide and hydrogenated at room temperature and atmospheric pressure for 36 hours. Uptake of hydrogen was 5,900 cc. After filtering and concentrating the oily residue was distilled. Yield of N-methyl-*cyclo*heptylamine, 29.7 g. (87% theoretical), b.p. 61—62°C./12 mm.

15 g. of the N-methyl-*cyclo*heptylamine was dissolved in dry toluene (100 ml.) and treated with chloroacetonitrile (10.7 g.) in the presence of anhydrous potassium carbonate (36.2 g.) with stirring. The mixture was heated under reflux for 24 hours, cooled, filtered and the filtrate dried over potassium carbonate. After concentration under reduced pressure, the residue was distilled affording N - methyl - N - *cyclo*-heptylamino-methyl cyanide. Yield 14.3 g. (73% theoretical), b.p. 74—77°C./0.4 mm.

10 g. of the N - methyl - N - *cyclo*heptylamino - methyl cyanide in dry ether (50 ml.) was added to a slurry of lithium aluminium hydride (2.7 g.) in dry ether (200 ml.) with cooling and stirring. Stirring was continued for 1½ hours at room temperature and in succession were then added, wet ether (50 ml.), water (5 ml.), 20% sodium hydroxide (15 ml.) and water (15 ml.). After filtration, the filtrate was dried (potassium carbonate) and concentrated. The residual oil was distilled affording 7.9 g. (77% theoretical) of N-methyl-N-*cyclo*heptylamino-ethylamine, b.p. 60°C./0.15 mm.

EXAMPLE 3

Preparation of β-(N-methyl-N-*cyclo*-octylamino)-ethyl-guanidine sulphate

N - methyl - N - *cyclo* - octyl ethylenediamine (6 g., .033 mole) was added to a solution of S-methylisothiouronium sulphate (4.6 g., 0.165 mole) in aqueous ethanol (50 ml.). The mixture was heated under reflux for 18 hours and then concentrated under reduced pressure to about half volume. On cooling 2.8 g. of solid was deposited, m.p. 248—254°C., which was recrystallised from aqueous ethanol/ether, affording 2.3 g., m.p. 255—260°C. Addition of ether to the initial mother liquor precipitated 2.9 g. of solid which after two recrystallisations from aqueous ethanol gave 1.9 g., m.p. 256—260°C. Total yield of β - (N - methyl - N - *cyclo* - octylamino) - ethyl - guanidine sulphate 4.2 g. (47% theoretical).

The starting material was prepared as follows: *Cyclo*-octanone (25 g., .2 mole) was added to 33% ethanolic methylamine (26 ml.) and the mixture added to previously reduced platinum oxide (0.2 g.) in ethanol (20 ml.). The mixture was submitted to low pressure hydrogenation at room temperature and hydrogenation was complete after an uptake of 4,400 cc. of hydrogen in 18 hours. The catalyst was filtered and the filtrate concentrated on a steam bath at atmospheric pressure. The residue was distilled under water pump vacuo and the distillate, b.p. 78—80°C./12 mm. (24.3 g.), containing some unchanged ketone was dissolved in ether and treated with concentrated hydrochloric acid, (26 ml.). Some solid hydrochloride precipitated which was redissolved by the addition of a little water. The aqueous layer was separated and basified with 40% sodium hydroxide and extracted with ether (3 × 100 ml.). The ethereal layer was dried (with potassium carbonate), concentrated and distilled giving 17.3 g. of N - methyl - *cyclo* - octylamine, b.p. 90—92°C./20 mm.

The amine (17 g., 0.12 mole) was dissolved in dry toluene (200 ml.) and anhydrous potassium carbonate (35 g.) was added. Chloroacetonitrile (10 g., 0.13 mole) was slowly added with stirring, and the mixture was stirred and refluxed for 20 hours. After filtration and washing of the inorganic solids with dry benzene, the filtrate was concentrated under reduced pressure and the residue was distilled under a high vacuum.

Two fractions of respectively b.p. 92—94°C./0.07 mm. (7.3 g.) n_D^{23} 1.4850 and b.p. 100—102°C./0.1 mm. (9.0 g.), n_D^{23} 1.4858, were collected and were shown by infra-red analysis to be almost identical and conform with N-methyl-N-cyanomethyl-*cyclo*-octylamine. Total yield 16.3 g., (75% theoretical).

The nitrile (16.3 g., 0.091 mole) was added dropwise to a slurry of lithium alu-

minium hydride (3.9 g.) in dry ether (100 ml.) with cooling and stirring. After addition, stirring was continued for 2 hours at room temperature and then the mixture refluxed for 1½ hours. Water (4 ml.), 20% sodium hydroxide (12 ml.) and water (12 ml.) were then added successively with cooling and stirring and after one hour at room temperature the resulting white solid was filtered and washed with ether. The combined filtrate was dried over potassium carbonate. After concentration under reduced pressure the residue was distilled, affording 12.8 g. (77% theoretical) of N-*cyclo*-octyl-N-methyl-ethylenediamine, b.p. 75—76°C./0.1 mm.

EXAMPLE 4

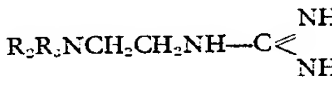
Preparation of N-amino-N¹-[2-(octahydro-1-azocinyl)-ethyl]-guanidine hydriodide.

2 - (Octahydro - 1 - azocinyl) - ethylamine (5.5 g.) dissolved in ethanol (20 ml.) was added to a solution of S-methyl-isothiosemicarbazide hydriodide (6.9 g.) in ethanol (80 ml.). The solution was heated under reflux for 20 hours and then concentrated *in vacuo* to 100 ml. The solution was filtered and to the resulting filtrate was added anhydrous ether until a slight permanent turbidity was produced. The solution was cooled in an ice bath and the solid which crystallised out was filtered. Yield 3.5 g., m.p. 117—122°C. Recrystallisation from iso-propanol-ether afforded 2.08 g. of white needles, without change in melting point. From the original mother liquor, 0.75 g. of solid was obtained of the same melting point. Total yield of N - amino - N¹ - [2 - (octahydro - 1 - azocinyl) - ethyl] - guanidine hydriodide, 4.25 g. (42% theoretical).

The starting material was prepared from octahydroazocine by treatment with chloroacetonitrile and reduction of the amino nitrile produced with lithium aluminium hydride by the methods described in Example 1.

WHAT WE CLAIM IS:—

1. Guanidine deriavtives represented by the general formula:—



and pharmaceutically acceptable acid addition salts, thereof, wherein R_1 is hydrogen or an amino group and wherein (a) when R_1 is hydrogen, R_2 is a methyl group and R_3 is a *cyclo*-heptyl or *cyclo*-octyl group, and (b) when R_1 is an amino group, R_2 and R_3 are joined together to form with the nitrogen atom a hexahydro-1-azepinyl group or an octahydro-1-azocinyl group.

2. Pharmaceutically acceptable acid addition salts of N - amino - N¹ - [2 - (hexahydro - 1 - azepinyl) - ethyl] - guanidine.

3. Pharmaceutically acceptable acid addition salts of β - (N - methyl - N - cycloheptylamino) - ethyl - guanidine.

4. Pharmaceutically acceptable acid addition salts of β - (N - methyl - N - cyclo - octylamino) - ethyl - guanidine.

5. Pharmaceutically acceptable acid addition salts of N - amino - N¹ - [2 - (octahydro - 1 - azocinyl) - ethyl] - guanidine.

6. N-Amino-N¹-[2-(hexahydro-1-azepinyl)-ethyl]-guanidine hydriodide.

7. β-(N-Methyl-N-cycloheptylamino)-ethyl-guanidine sulphate.

8. β-(N-Methyl-N-cyclo-octylamino)-ethyl-guanidine sulphate.

9. N-Amino-N¹-[2-(octahydro-1-azocinyl)ethyl]-guanidine hydriodide.

10. Process for preparing a pharmaceutically acceptable acid salt of a guanidine derivative having the formula defined in Claim 1, wherein R_1 is hydrogen, substantially as described in Example 2 or 3 of the foregoing Examples.

11. Process for preparing a pharmaceutically acceptable acid addition salt of a guanidine derivative having the formula defined in Claim 1, wherein R_1 is an amino group, substantially as described in Example 1 or 4 of the foregoing Examples.

12. A pharmaceutical composition comprising a guanidine derivative as claimed in any one of Claims 1 to 9 and one or more pharmaceutical diluents and/or excipients.

13. A composition as claimed in Claim 12, wherein the composition is made up in a dosage unit form.

HASELTINE, LAKE & CO.,
Chartered Patent Agents,
28, Southampton Buildings, Chancery Lane, London, W.C.2,
Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1964. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.